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Choosing new targets for rheumatoid arthritis therapeutics – too interesting to fail?

Iain B McInnes, Duncan Porter and Stefan Siebert

College of Medical, Veterinary and Life Sciences, University of Glasgow,
120 University Place,
Glasgow, G12 8TA

Contact:

E-mail: iain.mcinnnes@glasgow.ac.uk

Tel: +44 141 330 8412

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Progress in the treatment of Rheumatoid Arthritis (RA) in the last two decades has been remarkable, leading to substantial improvements in the quality of life for many patients. This has arisen from two fundamental developments. Firstly, the advent of pathogenesis-led therapeutics has generated a growing armamentarium of effective medicines available to the practitioner (1). The introduction of TNF inhibition arose from a careful *in vitro* cellular immunology and *in vivo* murine arthritis model programme that generated sufficient pre-clinical validation to encourage successful testing in RA of TNF inhibitors that had previously failed in sepsis studies. Subsequently, other therapies emerged that antagonise pro-inflammatory cytokines (for example, IL-6), inhibit T-cell costimulatory activation or deplete CD20 positive B-cells (1). More recently, a small molecule inhibitor of intracellular signalling in the form of the JAK1 / JAK3 inhibitor tofacitinib has heralded a new era of targeted synthetic DMARDs. A second substantial development has arisen from the advent of “strategically smart” approaches encapsulated in ‘treat early’ and ‘treat to target’ approaches (1). Together these developments have significantly improved the prognosis of patients with RA, reducing joint damage, functional disability, co-morbidity and mortality. Moreover, they have brought about the possibility of remission induction and maintenance of response in the treatment of RA, concepts which even two decades ago were inconceivable.

Midst such excitement it is salutary to consider briefly the cost of this journey of improvement and learn lessons to inform further progress. In particular, there have been numerous clinical targets selected on the basis of robust data sets which have failed to meet phase II or phase III trial success. This attrition rate may not be sustainable for either the pharmaceutical industry or the clinical trial community. This is pertinent since, in our view, there remains significant unmet clinical need in RA. True remission is still achieved only in a minority of patients and usually requires ongoing treatment with its attendant risks and significant financial cost. Moreover, there is a group of patients who become refractory to all existing therapies or who never respond in the first place. Against this background of unmet clinical need, rising drug development costs, yet burgeoning knowledge about

disease pathobiology, it is timely to reconsider the methodology that might lead to the accurate identification of novel immune targets for use in the treatment of RA.

The current edition of the journal contains a very interesting phase III clinical trial evaluating the use of the IL-17A inhibitor secukinumab in patients with active RA who have previously had an inadequate response to TNF inhibitors (2). The authors and editors alike are to be congratulated for bringing these data into the public domain – publishing such data comprises a significant step forwards in planning for success in the future. The trial examined the therapeutic impact of two doses of secukinumab compared with either abatacept or placebo. While the primary outcome was met at the “statistical level” for ACR20 improvement at week 24 for the higher 150 mg dose of secukinumab, this was achieved by only a modest proportion of patients, while significant improvement in key secondary endpoints was not achieved. Overall, the study demonstrates, at best, only modest superiority for secukinumab over placebo, with a response that was probably inferior to that seen with abatacept and does not support further development of secukinumab for use in patients with RA who have previously failed TNF-inhibitors. This study should be considered in the wider context of negative studies in RA for the IL-17 receptor inhibitor, which blocks IL-17RA (3), and modest benefits, at best, for ixekizumab, another IL-17A inhibitor (4). From this therapeutic trial set, we may conclude that IL-17A inhibition as monotherapy does not represent a satisfactory target for the treatment of RA.

It is worth considering the experimental narrative that brought us to the present phase III clinical trial. Interleukin 17A is a member of a large cytokine family that contains both pro- and anti-inflammatory members. It exhibits highly plausible biological effector functions, working either alone or especially in synergy with other inflammatory cytokines, such as TNF and IL-1, to promote synovial fibroblast activation, neutrophil activation and recruitment, B cell activation and antibody production and a variety of pro-destructive effects via osteoclast maturation and effector function (5). *In vivo* experiments in relevant inflammatory arthritis models suggested that IL-17A occupies a

position of hierarchical primacy, rendering it an attractive therapeutic target. The concept that Th17 cells have dominant roles in a range of autoimmune murine models is now well-established and, together with the demonstration of IL-17A expression in human tissues of clinical relevance, has led to the adoption of IL-17A as a therapeutic target in a range of cutaneous, gastrointestinal, neurologic and articular immune mediated diseases (5).

These observations have translated into rather mixed clinical results when appropriate human clinical trials have been performed (6). Thus IL-17A blockade in psoriasis yields remarkable clinical responses, with PASI100 rates close to 50% representing complete clearance of disease. Successful trials have been conducted in psoriatic arthritis (7–9) and axial spondyloarthritis (10), but with less spectacular musculoskeletal responses when compared to those achieved in skin (11). In contrast, no benefit accrued in patients with Crohn's disease upon receipt of secukinumab (12). From these studies we draw a number of conclusions. Firstly, the emerging group of IL-17A inhibitors represent a new class of medicines with viable pharmacologic and pharmacodynamic properties. Second, secukinumab and indeed other IL-17 inhibitors can be highly effective when used to treat disease states in which IL-17A enjoys functional hierarchical supremacy, such as cutaneous psoriasis. Thirdly, we have learned again from these studies that simply identifying an inflammatory cytokine as a potential target through documenting its presence in clinical tissues of relevance, postulating plausible biologic effector functions, is not sufficient to guarantee future therapeutic success. Moreover, we have learned once again that animal models of arthritis, whilst helpful in allowing us to dissect intact immune systems, have distinct translational limitations. Finally, the data suggest the value in building a compendium of trial outcomes across different inflammatory immune targets and immune mediated diseases to drive us towards a molecular taxonomy for inflammation medicine which could eventually complement the clinical phenotyping upon which current clinical trialling is based.

Where does this leave us in terms of current clinical target selections in RA? Happily, the field continues to progress with targets selected across a range of immune pathways. These include agents designed to inhibit innate immune activation, for example, those targeting Toll-like receptors and the intracellular molecular machinery that allows innate immune activation, for example, the inflammasome. There are ongoing efforts to develop new effector cytokine inhibitors, including “look alike” agents targeting both IL-6 receptor and IL-6 ligand and novel agents targeting GM-CSF or its receptor α subunit. Other JAK inhibitors are emerging including baricitinib, a JAK 1/2 inhibitor (13,14), and filgotinib, a JAK1 inhibitor (15,16). There is also interest in developing novel small molecule inhibitors of cellular signalling pathways, for example, inhibitors of the PI3 kinase family, BTK and also some interesting studies looking at epigenetic modifiers. The search for immunological homeostasis continues - it is worth noting the development of cellular therapies, for example, the transfer of tolerogenic dendritic cells and also immune therapeutics designed to achieve the same effect *in vivo*, for example, using drug loaded liposomes. Rather innovative approaches, such as those targeting the PAD enzyme system, stimulating the vagal nerve stimulation and modulating the neuroendocrine inflammatory system using gonadotropin releasing hormone antagonists (e.g. cetrorelix) have offered provisional evidence of benefit. This plethora of potential targets may well yield new opportunities, however what marks all of them is the absence of a definitive, consistently applied discovery pathways that can give high levels of confidence *a priori* that they will either target a hierarchically sufficiently prominent molecule or a particularly vulnerable point in the inflammatory cascade (17).

How then could we change our approach to the development of new therapeutic agents whilst celebrating the successes annotated above? It is important to recall the failure of clinical trials in RA that targeted, for example, CD4, CD5, IL-1, IL-12, IL-20 and IL-23. These clinical trial development programmes all arose from rational and plausible pre-clinical biological packages and, although there were subtle differences between the weight of evidences and the nature of the experimental systems employed, few could be considered to be rash development decisions based on the

knowledge of that time. Perhaps it is now appropriate to consider a systems-based approach to the development and validation of targets. We currently possess unparalleled access to digital information and computational power. When brought together with the depth of biologic experimentation possible at the molecular and cellular level to generate high volume and quality of data, this offers intriguing and powerful possibilities. Specifically, it may be possible to interrogate potential future therapeutic targets using *in silico* models of the rheumatic disease state, reflecting the accumulation of knowledge from pre-clinical biology studies, many clinical trials and *ex vivo* biomarker programmes, whether successful or not.

Comprehensive datasets can be generated that describe the genome, epigenome, transcriptome, proteome and metabolome from a range of biological samples – the so called “polyome”. Bioinformatics algorithms capable of integrating the discrete information contained across the polyome are emerging. Such data can be contributed from *in vivo* animal model studies in which pathways have been specifically targeted, together with *in vitro* leukocyte and synovial biology studies in which complex cellular contributions can be explored along with the signal pathways that subserve such biology. This should permit the creation of computational models that mimic RA pathways of inflammation and damage accrual that in turn, can be targeted *in silico* to estimate the likely outcomes of novel interventions. In parallel, mode of action studies in RA patients in which blood and synovial responses to interventions should be mandatory so as to gather new *ex vivo* datasets that can be fed into the models to offer refinement on an ongoing basis.

This systems approach to target discovery and validation could be usefully coupled with an increasing move towards stratification of the clinical and molecular phenotype of RA to improve success rates in the longer term. We should give greater deference to the stage of disease for which a drug is to be developed – it is probably reasonable to assume that the immune system will adapt over time as articular damage accrues in RA and our approaches should be amended accordingly. Models will be required therefore for early disease but may equally be required as we consider

development of agents for refractory RA. For the latter we especially need to understand the mechanisms that underpin therapeutic failure and acquired loss of response. As we come to recognise the molecular heterogeneity of RA, so we will recognise the value of enriching the likelihood of responses to a given target by appropriate clinical selection of patients for trial entry. Similarly, adaptive trial designs may allow us to more quickly discard ineffective therapies and direct patients within the trial to those agents to which they are more likely to respond. In this respect, it is likely that important lessons can be learned, and adapted, from the rapidly expanding use of immunotherapies and innovative trial designs emerging in the treatment of cancer. Taken together, if we are more prepared to learn from unsuccessful trials and to perform detailed mechanistic analysis, not only of why studies have succeeded, but also of why others have failed, we will enrich the possibilities for future generations as they meet the challenges of the “RA disease” that we will bequeath to them.

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